



RESTORATION OF VISUAL ACUITY AND VISUALLY GUIDED BEHAVIOR IN AMBIENT WHITE LIGHT WITH PHOTOSWITCHABLE SMALL MOLECULES

R. Sortino^{1,2,3}, *A. González-Díez*⁴, *S. Milla-Navarro*^{5,6}, *J. Martínez-Tambella*^{1,2,3}, *V. Paleo-García*^{5,6}, *E. Calatayud*¹, *P. de Saralegui*¹, *E. Opar*^{1,2,3}, *À. Claparols*¹, *J.A. Quintanilla*¹, *X. Martínez-Soler*¹, *F. Riefolo*^{1,2,3}, *C. Matera*^{1,3}, *J. Hernando*⁷, *A.M.J. Gomila*^{1,2,3}, *G. Pérez-Batlle*⁸, *C. Pereira*⁸, *N. Camarero*^{1,3}, *C. Serra*⁴, *X. Gómez-Santacana*⁴, *A. Llebaria*^{4,9}, *X. Rovira*⁴, *P. de la Villa*^{5,6}, *P. Gorostiza*^{1,3,10}

¹Institute for Bioengineering of Catalonia (IBEC), Barcelona, Spain, ²University of Barcelona Doctorate Program, Barcelona, Spain, ³CIBER-BBN, Madrid, Spain, ⁴Institute for Advanced Chemistry of Catalonia (IQAC-CSIC), Medicinal Chemistry and Synthesis (MCS) Laboratory, Barcelona, Spain, ⁵University of Alcalá de Henares (UAH), Alcalá de Henares, Madrid, Spain, ⁶Institute Ramón y Cajal of Health Research (IRYCIS), Madrid, Spain, ⁷Autonomous University of Barcelona (UAB), Barcelona, Spain, ⁸Fundació Eduard Soler, Ripoll, Girona, Spain, ⁹Institute for Advanced Chemistry of Catalonia (IQAC-CSIC), Synthesis of High Added Value Molecules (SIMChem), Barcelona, Spain, ¹⁰Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain

Category

Abstract Category: Scientific Research Abstract

Topic & Theme selection

Main Topic: D.4.a: Retina

Secondary Topic: G.19: Rare Diseases

Abstract Body

Abstract body: Blinding diseases caused by photoreceptor (PhR) degeneration, such as geographic atrophy (GA) secondary to dry age-related macular degeneration and retinitis pigmentosa (RP), leave most inner retinal circuitry structurally intact but unable to respond to light. Current therapeutic options remain limited. Gene therapy benefit only small, mutation-defined subsets of RP patients, while electronic retinal prostheses are invasive, costly, and provide limited visual resolution. Photopharmacology can develop photoswitchable small molecules to restore vision impairment by conferring light sensitivity to ion channels that are widely expressed in the remaining inner retinal neurons, and a first-in-human clinical trial is ongoing. Here, we developed novel photoswitchable small molecule ligands of metabotropic glutamate 6 (mGlu₆) receptors, which are located exclusively at the dendrites of ON bipolar cells (postsynaptic to PhRs), leveraging a privileged position to mimic physiological signals in the remnant retinal circuit. These photoswitchable ligands (prothe6) act as 'molecular prostheses' and can restore the light input to the retina *via* upstream-targeted control of the circuit after PhRs degeneration. Prothe6 are allosteric, drug-like, water soluble, and display outstanding *in vitro* properties including full efficacy, nanomolar potency, fast deactivation in ambient white light, and fast reactivation in the dark. *In vivo* experiments show recovery of visual acuity of blinded zebrafish larvae and restoration of innate light-avoidance behavior in mouse models of GA and RP, with effects confirmed to be mGlu₆ mediated. In addition, at least two compounds restore sight by topical administration and display promising safety properties, supporting their potential as drug candidates for degenerative blinding diseases.

Keywords

Keywords: Yes

Keyword 1: photopharmacology

Keyword 2: retinal degenerative diseases

Poster Group Code

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